REMARKS

Upon entry of the present amendment, claims 6, 13-17, and 19-25 are pending in this application. Claims 1-5, 7-11, 12, 18, and 26-34 are cancelled. Claims 6, 17, and 19-20 are amended to recite inversion of the target and recombinase genes. Support for the amendments made herein can be found at least at page 6, lines 25-28, page 7, lines 8-17, and page 8, lines 8-19. As such, no new matter is added.

Rejections under 35 U.S.C. §103

Claims 6, 13, 14, 17, 21, 24, and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Baszczynski et al. US Patent No. 6,187,994, referred to as "Baszczynski," in view of Qin et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:1706-1710, referred to as "Qin." Claims 15 and 16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Baszczynski in view of Qin and further in view of Fitzmaurice et al WO 93/07257, referred to as "Fitzmaurice." The Examiner states that amended claim 6 does not specify that the target gene comprised by the second nucleic acid molecule is the same target gene modulated in the method (i.e. "a target gene" recited in the preamble).

Independent claim 6, from which all other claims subject to the rejection properly depend, has been amended to incorporate the limitations of cancelled claim 18 as stated by the Examiner. Specifically, claim 6 has been amended herein to require that the target gene sequence of the second nucleic acid that is modified by the recombinase is also inactivated. As such, Applicants submit that the rejection is moot with respect to the claims as amended and should be withdrawn.

Claims 6, 17, and 19-23 are rejected under 35 U.S.C. §103(a) as being unpatentable over Moller et al. US Patent No. 6,723,896 B1, referred to as "Moller." Applicants traverse the rejection with respect to the claims as amended.

Independent claim 6, from which all other claims subject to the rejection properly depend, has been amended to delete the terms "excise" and "excision" and to recite the terms "invert" and "inversion" with respect to the second nucleic acid. Dependent claim 17 has been amended to recite that the signal sequences of the second nucleic acid are in inverted orientation which leads to inversion of the genes and regulatory elements that are captured in between these

signal sequences. Dependent claims 19 and 20 have been amended to delete the term "excision" and to recite the term "inversion."

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moller teaches a method of modifying a target gene by introducing a nucleic acid comprising a first nucleic acid comprising a recombinase gene and a second nucleic acid comprising a target gene and regulatory elements flanked by signal sequences that are recognized by the recombinase, which excises the target gene (constructs of Figure 1). Moller does not teach a critical element of the instant invention--the self-extinguishing recombinase feature of the instant claims. The constructs of Figure 1 as taught by Moller do not comprise a recombinase gene flanked by signal sequences and, hence, expression of the recombinase does not lead to inactivation of the recombinase as required by the claimed invention.

Moller further describes a second series of constructs which modulate transgenes, e.g. sequences that are incorporated into the plant genome, called suicide cassettes (Figures 4 and 5). Moller describes methods of excising inserted silent transgenes, or stuffer fragments, from the genomic sequence in order to activate genes. Moreover, Moller teaches methods of *activating* genes by inverting transgenes that had previously been inserted into the genome in an antisense orientation. Critically, Moller does not teach *inactivation* of genes by inversion of sequences.

In order for a *prima facie* case of obviousness to be made, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Applicants submit that Moller fails to disclose all limitations of the instant claims as amended. As stated by the Examiner in the instant Office Action at page 8, "Moller et al. does not explicitly teach the inclusion of signal sequences recognized by the recombinase in the first nucleic acid molecule such that the expression of the recombinase excises a sequence from the first nucleic acid molecule resulting in modulation of expression of the recombinase gene" as required by the instant claim 6. As such, Moller necessarily fails to teach, suggest, or demonstrate that signal

sequences for the first nucleic acid and the second nucleic acid are not the same sequences, as further required by the instant claim 6. Critically, Moller fails teach, suggest, or demonstrate placement of signal sequences flanking the target gene and regulatory elements thereof in an inverted orientation such that expression of the recombinase leads to inactivation of these sequences as required by the instant claim as amended. The claimed invention further requires that signal sequences for the first nucleic acid and the second nucleic acid are not the same sequences. The constructs of Moller do not employ more than one type of signal sequence. This difference is greater than a mere duplication of parts because the required addition is qualitatively different than what is already present in the construct.

Furthermore, to show *prima facie* obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Moller teaches methods of gene inactivation by insertion of "stuffer fragments." Moller consequently teaches methods of gene excision which lead to gene activation, e.g. removal of previously incorporated stuffer fragments or silent transgenes. Moller also teaches methods of inserting silent transgenes within the plant genome in antisense orientations. Consequently, Moller teaches methods of gene inversion to activate expression of previously incorporated silent transgene expression, e.g. inverting orientation of these transgenes from antisense to sense. The essence of the Moller invention is to insert a silent or inactive gene into a plant cell and then to introduce a construct to activate that gene by recombination. The recombinase is not necessarily inactivated.

The intended purpose of the present invention is contrary to that of Moller. The claimed methods teach introducing active genes and a recombinase into plant cells which provide a therapeutic gene product for a desired amount of time until the provided recombinase shuts down expression of the active target gene *and* the recombinase itself. Moller fails to teach methods of gene inactivation using gene inversion. Furthermore, Moller fails to combine gene inactivation, gene inversion, and a self-excising recombinase in the same construct. Moller does not teach or suggest a method of gene *inactivation* in which a target gene is *irreversibly inverted* by a *self-excising* recombinase. In fact, Applicants submit that Moller teaches away from the claimed invention.

Contrary to the claimed methods, which require that the sequence inverted in the second nucleic acid molecule, e.g. the target gene, is inactivated, Moller only describes methods of *activating* genes by inverting sequences. The only description provided by Moller for

inactivating genes involve inserting silent transgenes (Figures 4 and 5) and excising stuffer fragments (Figure 1). However, Moller himself recognized that these constructs had the disadvantage that the recombination event was reversible and would not lead to the complete inactivation of the gene. Moller states at column 6, lines 11-19, "Timed expression of the recombinase leads to site-specific inversion of the transgene into a sense orientation which in turn leads to transgene activation. This approach, although feasible, has the disadvantage that the recombination event is reversible due to the continual presence of both recombination sites after recombination. This in effect means that the intervening DNA fragment can be "flipped" back and forth during the presence of the recombinase" (see Figure 3 of Moller). As such, Applicants submit that Moller teaches away from the use of inversion as a mechanism of gene inactivation. As such, one of ordinary skill in the art would not be motivated to combine the teachings of Moller to reach the present invention.

Moreover, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one ordinary skill in the art. *See* MPEP §2143.01, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385, 1396 (2007). Moller, himself recognized that it would be desirable to remove/inactivate transgenes from transgenic plants (See, Moller at column 2 and Office Action at page 9) Moller further recognized the problem with his method in that inversion of transgenic sequences in the presence of a recombinase leads to flipping of the inverted sequences and therefore would not result in total inactivation of the gene. Notwithstanding his desire to inactivate transgenes and his identification of the problem with using inversion to do so, Moller himself did not predict that the Moller constructs could be modified to solve his problem and arrive at the claimed invention.

Accordingly, Applicants submit that there is no objective reason provided in Moller, that would lead the skilled artisan to arrive at the claimed invention. Moreover, there is no evidence that the results of combining the elements of the Moller constructs would have been predictable, particularly in light of the inability of Moller himself, to identify and successfully use these elements to inactivate a gene. Thus, any suggestion that it would have been obvious that the inclusion of lox sites flanking the recombinase gene would result in excision of the recombinase and inversion of the target sequence is an improper application of hindsight based on Applicants' disclosure in the instant application. Thus, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness and request that this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and a Notice of Allowance for the pending claims is respectfully requested. If there are any questions regarding this application that can be handled in a phone conference with Applicants' Attorneys, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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